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AMENDMENT & RESPONSE Address to: Commissioner for Patents Washington, D.C. 20231	Application Number	09/628,472
	Attorney Docket Number	10003511-1
	Filing Date	July 31, 2000
	First Named Inventor	Wolber
	Examiner	B. Forman
	Group Art	1655
	Title	Array Based Methods for Synthesizing Nucleic Acid Mixtures

Sir:

This amendment is responsive to the First Office Action dated October 3, 2001 for which a three-month period for response was given making this response due on or before January 3, 2002. In view of the amendments to the claims and the remarks put forth below, reconsideration and allowance are respectfully requested.

AMENDMENTS

IN THE CLAIMS

1. (Once Amended) A method for producing a mixture of nucleic acids, said method comprising:

(a) providing an array of distinct single-stranded probe nucleic acids of differing sequence where each distinct probe present on said array comprises a constant domain and a complement variable domain;

(b) hybridizing nucleic acids complementary to said constant domain with said array of single-stranded probe nucleic acids to produce a template array of overhang comprising duplex nucleic acids, wherein each overhang comprising duplex nucleic acid of said array comprises a double-stranded constant region and a single-stranded variable region overhang; and

(c) subjecting said template array of overhang comprising duplex nucleic acids to primer extension reaction conditions under conditions sufficient to produce said mixture of nucleic acids.

5. (Once Amended) A method for producing a mixture of a plurality of distinct deoxyribo-oligonucleotides of differing sequence, wherein each distinct deoxyribo-

oligonucleotide of said plurality comprises a different variable domain V, said method comprising:

(a) providing an array of a plurality of surface immobilized distinct single-stranded probes, wherein each distinct surface immobilized single-stranded probe present on said array is described by the formula:

surface-L-R-F-cV-5'

wherein:

L is an optional linking domain;

R is a recognition domain;

F is a functional domain; and

cV is a complement domain having a sequence that hybridizes under stringent conditions to a variable domain of one of said distinct oligonucleotides of said plurality;

(b) contacting said array of a plurality of surface immobilized distinct single-stranded probes under hybridization conditions with a population of nucleic acids of the formula:

5'-cR-cF-3'

wherein:

cR is the complement of R; and

cF is the complement of F;

whereby a template array of overhang comprising duplex nucleic acids is produced, wherein each overhang comprising duplex nucleic acid of said array is described by the formula:

surface-L-R-F-cV-5'

| |

5'-cR-cF-3'; and

(c) subjecting said template array of overhang comprising duplex nucleic acids to primer extension reaction conditions;

to produce said mixture of a plurality of distinct deoxyribo-oligonucleotides of differing sequence, wherein each distinct constituent of said plurality comprises a different variable domain V.

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8. (Once Amended) The method according to Claim 5, wherein said recognition

a3 cont domain is a recognized by a restriction endonuclease.

14. (Once Amended) The assay according to Claim 13, wherein said target nucleic acids are labeled.

a4

15. (Once Amended) The assay according to Claim 13, wherein said assay further comprises washing unbound target away from the surface of said array.

REMARKS

Applicants respectfully request reconsideration of the application and allowance of Claims 1-15 (the only pending claims currently under examination) in view of the amendments and remarks made herein.

Amendments

Claim 1 has been amended to clarify the language in the "hybridizing" step (b). Claim 5 has been amended to remove the term "constituent" from the preamble and otherwise clarify the language of the claim. Claim 8 has been amended to correct a typographical error and Claims 14 and 15 have been amended to correct their dependency onto Claim 13.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached is captioned **"VERSION WITH MARKINGS TO SHOW CHANGES MADE."** As can be seen, no new matter has been added.

As such, entry of the above amendments is respectfully requested.

Substitute Specification

In accordance with the Examiner's request, enclosed with this response is a substitute specification under 37 C.F.R. § 1.125(a).

Objections

Claims 1 and 8 were objected to for typographical errors. In view of the above amendments to these claims, it is believed that these objections have been addressed.

Rejections

Claims 1-15 were rejected under 35 U.S.C. § 112, 2nd ¶ for a number of reasons. Each of these reasons is addressed separately below.

a. The Examiner asserts that Claims 1-4, 14, and 15 are indefinite because they recite contacting under hybridization conditions. Solely in order to expedite prosecution of this case, the language of these claims has been changed to "hybridizing" in accordance with the Examiner's suggestion.

b. The Examiner asserts that Claims 1-4, 14 and 15 are indefinite for use of the phrase "subjecting said template array... to primer extension reaction conditions...." for the asserted reason that it is unclear whether the recitation is a method step of primer extension.

The law is clear that "[i]f the claims, read in the light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more." North American Vaccine, Inc. v. American Cyanamid Co. 28 USPQ 2d 1333, 1339 (Fed. Cir. 1993), cert. Denied, 114 S. Ct. 1645 (1994).

In the present case, the specification teaches beginning at page 10, line 25 and extending to page 13, line 14, what is meant by this phrase. This phrase of the claim, when read in light of these pages of the specification, is completely clear and not indefinite.

As such, the Examiner is requested to withdraw this rejection.

c. It is believed that this rejection to Claim 5 has been overcome by the above amendments.

d. With respect to the terms "recognition domain" and "functional domain," it is asserted that these terms are clear and definite to those of skill in the art when read in view of the specification, see e.g., page 7, line 23 to page 8, line 7, where both of these domains are defined and described in greater detail. As such, this rejection may be withdrawn.

e. It is believed that this rejection has been overcome by the above amendment changing the dependency of these claims to depend on Claim 13.

f. It is believed that this rejection has been overcome by the above amendment changing the dependency of these claims to depend on Claim 13.

g. It is believed that this rejection has been overcome by the above amendment changing the dependency of these claims to depend on Claim 13.

In view of the above remarks and amendments, the Examiner is respectfully requested to withdraw the rejections to Claims 1 to 15 under 35 U.S.C. § 112, 2nd ¶.

Claims 1-4, 10-12 and 14 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Cantor.

In making this rejection, the Examiner sites to the section of Cantor from Col. 13, line 41 to Col. 14, line 22 of which reads:

> Alternatively, probe arrays may also be made which are single-stranded. These arrays are created, preferably on a solid support, basically as described, by synthesizing an array of nucleic acids each comprising a constant sequence of length C at a 3'-terminus and a random sequence of length R at a 5'-terminus, and fixing the array to a first solid support. Arrays created in this manner can be quickly and easily transformed into double-stranded arrays by the synthesis and hybridization of a set of nucleic acids with a sequence complimentary to the constant sequence of the replicated array to create a double-stranded replicated array. However, in their present form, single-stranded arrays are very valuable as templates for replication of the array.

> Due to the very large numbers of probes which comprise most useful arrays, there is a great deal of time spent in simply creating the array. It requires many hours of nucleic acid synthesis to create each member of the array and many hours of manipulations to place the array in an organized fashion onto any solid support such as those described previously. Once the master array is created, replicated arrays or slaves, can be quickly and easily created by the methods of the invention which take advantage of the speed and accuracy of nucleic acid polymerases. Basically, methods for replicating an array of single-stranded probes on a solid support comprise the steps of synthesizing an array of nucleic acids each comprising a constant sequence of length C at a 3'-terminus and a random sequence of length R at a 5'-terminus, fixing the array to a first solid support, synthesizing a set of nucleic acids each comprising a sequence complimentary to the constant sequence, hybridizing the nucleic acids of the set with the array, enzymatically extending the nucleic acids of the set using the random sequences of the array as templates, denaturing the set of extended nucleic acids, and fixing the denatured nucleic acids of the set to a second solid support to create the replicated array of single-stranded probes.

The Examiner asserts that the above section teaches all of the elements of Claim 1.

However, Claim 1 is directed to a method of producing a mixture of nucleic acids. The term mixture is defined as: "A composition of two or more substances that are not chemically combined with each other and are capable of being separated." *The American Heritage® Dictionary of the English Language, Fourth Edition Copyright © 2000 by Houghton Mifflin Company.*

Thus, the claimed methods are methods of producing a single heterogenous population of a plurality of distinct nucleic acids.

In the cited Cantor section, Cantor is concerned with replicating an initial array of nucleic acids. Arrays of nucleic acids are structures in which a plurality of different nucleic acids are attached to a surface at different, known locations. As such, the array is not a "mixture" of nucleic acids in that it is not a heterogenous composition of nucleic acids, but is instead a plurality of individual homogenous nucleic acid compositions.

In Cantor's replicating process, while he does employ primer extension, he never

mixes the products to produce a mixture because he lays the products down on a new substrate to produce the replicated array. In other words, he keeps each primer extension product separate from the others so that the replicated array can be produced. If this were not the case, the product produced by the taught method would not be a replicated array.

Therefore, Cantor does not teach a method of producing a mixture of nucleic acids as claimed.

As such, Cantor fails to teach all of the elements of Claim 1 and therefore fails to anticipate this claim. In addition, since Claims 2-4, 10-12 and 14 incorporate all of the limitations of Claim 1, Cantor fails to anticipate these claims as well.

Accordingly, Claims 1-4, 10-12 and 14 are not anticipated under 35 U.S.C. § 102(b) by Cantor and this rejection may be withdrawn.

Claims 5-9 and 13 have been rejected under 35 U.S.C. § 103(a) as being obvious over Cantor in view of Dattagupta.

Claim 5 includes all of the steps of Claim 1. As pointed out above, Cantor fails to teach the production of a mixture of nucleic acids as claimed. In addition, Cantor fails to suggest such a method because Cantor is concerned with replicating arrays, where one must keep all of the different populations of primer extension products separate so that they can be placed on a substrate to produce the replicated array. As such, Cantor teaches away from producing a mixture of nucleic acids.

Dattagupta appears to have been cited solely for the teaching of a functional and recognition domain. As such, Dattagupta fails to make up the above deficiency in the Cantor teaching.

Because the combined teaching of Cantor and Dattagupta fails to teach a method of producing a mixture of nucleic acids with an array, Claims 5-9 and 13 are not obvious over the combined teachings of these references and this rejection may be withdrawn.

Finally, enclosed with this response is a sequence listing.

Conclusion

The applicant respectfully submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone Gordon Stewart at 650 485 2386. The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-1078.

Respectfully submitted,

Date: 2.4.02

By: _____
Bret E. Field
Registration No. 37,620

encs

- Substitute specification under 37 C.F.R. § 1.125(a).
- Sequence Listing